REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

By the foregoing amendment, claim 22 has been amended to recite that the claimed inhibitor of *Helicobacter pylori* colonization "consist[s] of the glycoprotein according to Claim 16." Support for such amendment can be found throughout the originally filed application. Thus, no new matter has been added.

Turning now to the Official Action, the Examiner has acknowledged that the Japanese application to which applicants' claim priority, and thus submitted the English language translation of, is No. 2000-113913, not No. 2000-113912 as indicated in the April 4, 2002 Official Action. The Examiner has indicated that unfortunately the certified copy of the Japanese application is not in the file of the U.S. Patent and Trademark Office and, thus, requested applicants to provide a photocopy of the priority document. Applicants' representative is in the process of attempting to obtain a photocopy of the priority document. Upon receipt thereof, applicants' representative will promptly forward a photocopy to the Examiner.

Applicants acknowledge the Examiner's statements that the previous rejection of claims 16-20 and 22-26 under the judicially created doctrine of obviousness-type double patenting as well as the previous rejection of claim 25 under 35 U.S.C. § 112, second paragraph, are withdrawn.

The Examiner has rejected claim 22 under 35 U.S.C. § 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly the subject matter which applicant regards as the invention. This rejection is respectfully traversed. However, to expedite prosecution in the subject application, and not to acquiesce to the Examiner's rejection, claim 22 has been amended to recite that the inhibitor "consist[s] of the glycoprotein . . . ." In view of the above, the Examiner is respectfully requested to withdraw this rejection.

Claims 16 and 22-26 have been rejected under 35 U.S.C. § 102(b) as purportedly being anticipated by Peterson et al (U.S. Patent No. 5,505,955) (hereinafter "the '955 patent").[1] This rejection is also respectfully traversed.

Applicants' claimed invention is based on the finding that urease of *Helicobacter pylori* functions as an adhesion for the colonization in the stomach, and the glycoprotein capable of specifically binding to *Helicobacter pylori* urease are remarkably effective for elimination of *Helicobacter pylori* from the stomach when used even in a small amount. There are many kinds of glycoproteins having different compositions, structures or properties in milk. The glycoprotein of the present invention is obtained by contacting a glycoprotein-containing substance with *Helicobacter pylori* urease and isolating and

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[1] The Examiner has stated on page 4 of the Official Action that "[c]laims 17-21 are rejected because they are dependent from a rejected claim." It is unclear whether they are rejected under 35 U.S.C. § 102(b) over the '995 patent or they are objected to for being dependent upon a rejected base claim. In any event, this rejection and/or objection is respectfully requested to be withdrawn since, for the reasons described herein, the '995 patent fails to disclose a glycoprotein which specifically binds to urease as provided for in claims 17-21 by being directly or indirectly dependent upon claim 16.

purifying the glycoprotein specifically bound to the urease, for example, using an affinity chromatography. Therefore, the glycoprotein of the present invention masks the adhesion of *Helicobacter pylori* (urease) and exhibits remarkable effects on the inhibition of *Helicobacter pylori* urease adherence to gastric mucosa, thereby inhibiting *Helicobacter pylori* colonization in the stomach.

The Federal Circuit has held that for prior art to be anticipatory, every element of the claimed invention must be disclosed, either expressly or inherently, in a single item of prior art in the form literally defined in the claim. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 213 U.S.P.Q. 81, 90 (Fed. Cir. 1986). This requirement for anticipation has not been met with respect to the claims of the present application.

The '955 patent fails to expressly disclose every element of the claimed invention as it fails to disclose at least a glycoprotein which specifically binds to urease of *Helicobacter pylori*. The Examiner, however, attempts to argue that the '955 patent discloses a glycoprotein that inherently possesses the properties of applicants' claimed glycoprotein.

It is well established that anticipation of inventions set forth in product claims cannot be predicated on mere conjecture respecting the characteristics of products that might result from the practice of processes disclosed in references. *See, e.g., W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 220 U.S.P.Q. 303, 314 (Fed. Cir. 1983); *Ex Parte Standish*, 10 U.S.P.Q.2d 1454, 1457 (U.S. PTO Bd. of Pat. App. & Int. 1989); *see also Ex Parte Skinner*, 2 U.S.P.Q.2d 1788, 1789 (U.S. PTO Bd. of Pat. App. & Int. 1987) (discussing that the mere fact that a certain thing may result from a given set of

circumstances is not sufficient as inherency may not be established by probabilities or possibilities). While the U.S. Patent and Trademark Office can require applicants to prove that the prior art product does not necessarily or inherently possess the characteristics of his claimed product, *see, e.g., Ex parte Maizel*, 27 U.S.P.Q.2d 1662, 1667-68 (U.S. PTO Bd. of Pat. App. & Int. 1993); *Ex Parte Gray*, 10 U.S.P.Q.2d 1922, 1925 (U.S. PTO Bd. of Pat. App. & Int. 1989), the Examiner must provide some evidence or scientific reasoning to establish the reasonableness of the Examiner's belief that the property is an inherent characteristic of the prior art before applicants can be put to this burdensome task. *See Ex Parte Skinner*, 2 U.S.P.Q.2d at 1789.

Applicants respectfully submit that the record does not contain a sufficient level of evidence or scientific reasoning necessary to require applicants to prove that the glycoprotein of the '995 patent does not necessarily or inherently possess the characteristics of applicants' claimed invention.

Furthermore, applicants submit that the glycoprotein disclosed in the '995 patent does not inherently possess the characteristics of the claimed invention. In particular, the glycoprotein disclosed in the '995 patent is not a glycoprotein which specifically binds to *Helicobacter pylori* urease. This is because the glycoprotein of the '995 patent is derived from milk fat globules (MFG), and the glycoprotein (mucin) derived from milk fat globules (MFG) has little inhibitory activity against *Helicobacter pylori* urease adherence to gastric

mucosa. In this regard, the Examiner's attention is directed to Exhibit A enclosed herewith.[2]

As shown in Table 1 of Exhibit A, mucin (glycoprotein) derived from milk fat globule membrane (MFGM), prepared as shown in FEMS Immunol. Med. Microbiol., 20:275-281 (1998), has high IG_{50} value, namely, little inhibitory activity against *Helicobacter pylori* urease adherence to gastric mucosa, and this seems to be caused by the fact that MFGM-derived glycoprotein contains primarily sialylated components. This data means that the glycoprotein derived from MFGM does not specifically bind to *Helicobacter pylori* urease.

Milk fat globules (MFG) comprises butter particles and milk fat globule membrane (MFGM). Glycoprotein is contained in membranes. Therefore, the glycoprotein derived from MFGM is substantially the same as that derived from MFG.

Thus, the glycoprotein disclosed in the '995 patent does not inherently possess the characteristics of applicants' claimed glycoprotein with respect to at least the inhibitory activity against *Helicobacter pylori* urease adherence to gastric mucosa. Hence, applicants' claimed invention is different from the 46kDa glycoprotein derived from MFG disclosed in the '995 patent.

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[2] Exhibit A is part of the material attached to the Amendment and Reply filed on September 12, 2000 in earlier-filed Application Serial No. 09/458,996, now U.S. Patent No. 6,235,709 (the same patent in which applicants filed a terminal disclaimer over in the present application).

As the '995 patent fails to either expressly or inherently disclose the claimed invention, the '995 patent does not anticipate applicants' claimed invention. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Applicants acknowledge the Examiner's statement that "claims 27-30 are free of the prior art and allowable."

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions relating to this Amendment and Reply, or the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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Date: January 22, 2003

I hereby certify that this correspondence is being sent by Facsimile Transmission to the Assistant Commissioner For Patents, Washington, D.C. 20231 on:

Date: January 22, 2003
Name: Jamyn Ebeling
(Typed or printed name of person signing the certificate)
Sign: _____
(Signature of person signing the certificate)
Date: January 22, 2003
(Date of Signature)

Application Serial No. 09/833,637
Attorney's Docket No. 011900-309

Attachment to Amendment and Reply dated January 22, 2003

Marked-up Claim 22

22. (Amended) An inhibitor of *Helicobacter pylori* colonization, [comprising as an active ingredient] consisting of the glycoprotein according to Claim 16.

EXHIBIT A

Experiment A

Comparison of IC_{50} values for mucin derived from whey of bovine milk used in the present invention, gastric mucin and mucin derived from fat globule membrane disclosed by Hirmo et al.

IC_{50} values were determined by the in vitro adherence inhibition assay that the present inventors had developed (Gastoenterol., Vol. 119, No. 2, 2000, see Fig. 2) for mucin derived from whey of bovine mucin (the present invention), mucin derived from fat globule membrane (prepared as described in the Hirmo et al.reference) and porcine gastric mucin (Sigma). As shown in Table 1, mucin derived from bovine milk whey had a remarkably low IC_{50} value, 3.9-4.5 μ g/ml and mucin derived from bovine fat globule membrane (MFGM) had high IC_{50} value, 324-397 μ g/ml. Porcine gastric mucin had high IC_{50} value,290.3. Thus, whey-derived mucin can inhibit H. pylori urease at a very low concentration, i.e., has a remarkably excellent ability for inhibition of H. pylori urease adherence to gastric mucin. This is because whey-derived mucin is considered to have primarily sulfated components and to inhibit the adherence of urease to sulfated components in gastric mucin thereby inhibiting the adherence of H. pylori to mucus layer on gastric mucosa. However, MFGM-derived mucin containing primarily sialylated components cannot inhibit fully the adherence of urease to gastric mucin, and therefore, MFGM-derived mucin is not considered to be useful for the adherence inhibition of H. pylori to mucus layer.

Table 1. Comparison of IC_{50} values for bovine mucins derived from milk whey and fat globule membrane, as determined by competitive adherence inhibition of the H. pylori urease-porcine gastric mucin complex

Mucin	IC_{50}(μ g/ml)
Bovine milk whey	
Sample 1	4.1
Sample 2	3.9
Sample 3	4.5
Bovine fat globule membrane(MFGM-1)[1)]	
Sample 1	397.3
Sample 2	323.8
Sample 3	351.9
Porcine gastric mucin	290.3
Positive control	
Dextran sulfate (Mr≈500,000)	46.3

1) prepared as shown in FEMS Immunol.Med.Microbiol.,20:275-281,1998

Fig. 1 pH-dependent Adherence of Urease to Gastric Musus and Mucin

Urease purified from H. pylori binds porcine gastric mucus and porcine gastric mucin purified from the gastric mucus only at acidic pH range with a peak at pH 4.0. This means that H. pylori urease functions as an adhesin in adherence of H. pylori to mucus layer on gastric mucosa under acidic pH conditions of the stomach, and that the receptor of urease is mucin in mucus layer. Inhibition of the binding between urease and mucin due to blocking of urease in the first step of H. pylori infection results in the inhibition of H. pylori adherence.

Fig. 2 Procedure for Competitive Adherence Inhibition Assay

The present inventors found that H. pylori urease is an adhesin in adherence of H. pylori to mucus layer on gastric mucosa which is a first step of H. pylori infection and H. pylori can adhere to gastric mucosa by adherence of urease to mucin in mucus layer on gastric mucosa (mucin is a receptor of urease). Based on the finding, the present inventors developed in vitro assay for determining the inhibitory activity of a substance to inhibit H. pylori adherence to gastric mucosa (Gastroenterology, Vol. 119, No. 2, 2000, in press). This assay can provide a concentration where binding between H. pylori urease and porcine gastric mucin at pH 4.0 is 50% inhibited (IC_{50}). In this assay the adherence reaction is carried out at pH 4.0, which reflects the acidic condition in the stomach, and therefore, this assay can screen a substance capable of inhibiting binding between urease as an adhesin and mucin as a receptor, i.e., inhibiting adherence of H. pylori to mucus layer on gastric mucosa which is a first step of H. pylori infection.